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BCG vaccination in South African HIV-exposed infants – risks and benefits

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Until 2007, the World Health Organization (WHO) recommended that bacille Calmette-Guérin (BCG) vaccination should be contraindicated in infants with symptomatic HIV disease in countries with a high burden of tuberculosis. This recommendation was based on the perceived low risk of serious adverse events in HIV-infected infants. The WHO revised its recommendations regarding BCG vaccination in HIV-infected infants in 2007, making HIV infection a full contraindication to BCG vaccination.¹ BCG induces protective efficacy against tuberculous meningitis of 73% (67 - 79%) and against miliary disease of 77% (58 - 87%) in HIV-uninfected children.² The efficacy against childhood pulmonary disease is variable;³ there is no evidence that BCG induces a protective effect against tuberculosis in HIV-infected infants and children.⁴ BCG is a safe vaccine in immunocompetent infants, and severe vaccine adverse events in HIV-uninfected infants occur only with rare primary immune deficiencies in approximately 1 per million vaccinees.⁵

The South African context and the risk of BCG adverse events in HIV-infected infants

BCG has been used in South Africa since 1973. Since 2001, a single dose of 0.05 ml BCG Danish strain (1331, Statens Serum Institute, Copenhagen) has routinely been given intradermally

in the right deltoid region at birth to all infants, consistent with WHO guidelines. In the Western Cape Province, BCG coverage was 99% in 2005.⁶

Recent evidence shows that South African HIV-infected infants receiving BCG vaccination at birth are at increased risk of developing BCG adverse events. Up to 6% of children enrolled in a public access HIV treatment programme in the Western Cape experienced local or regional BCG adverse events (BCG adenitis).⁷ The incidence of the most severe adverse events, systemic or disseminated BCG (dBCG), is estimated at 992 per 100 000 HIV-infected infants, typically occurring at a median age of 7 - 8 months and with an all-cause mortality of approximately 75%.⁸ Confirmed BCG dissemination has only been documented in infants with rapid HIV disease progression in the first year of life.⁹⁻¹¹

The Global Advisory Committee on Vaccine Safety (GACVS) and the Strategic Advisory Group of Experts (SAGE) reviewed data on BCG safety in HIV-infected infants in 2007 and recommended that BCG vaccination not be given to any HIV-infected infants, even in settings where tuberculosis is highly endemic.^{12,13} This revision was primarily based on the documented risk of dBCG disease in HIV-infected infants and not on the risk of local and regional BCG adverse events. Identification of HIV infection at birth, when BCG is often administered, is however not feasible owing to the limited sensitivity of early testing and the complicated logistics of repeat HIV-DNA polymerase chain reaction (PCR) testing. Routine diagnostic testing is performed from 6 weeks of age in South Africa and HIV-infected infants are usually asymptomatic at birth when given BCG.

BCG is also associated with immune reconstitution inflammatory syndrome (BCG IRIS), which usually presents as ipsilateral suppurative or non-suppurative regional adenitis following initiation of HAART. BCG IRIS, one of the most common forms of IRIS among South African HIV-infected infants, has low mortality but is associated with considerable morbidity.^{8,14-16} The southern African CHER trial of early versus delayed highly active antiretroviral therapy (HAART) in HIV-infected infants indicates that early initiation of HAART before 12 weeks of age and before clinical and immunological deterioration achieved a 76% reduction in infant mortality and a 75% reduction in HIV disease progression.¹⁷ Infants whose HAART was delayed until clinically or immunologically indicated had an incidence of BCG IRIS of 15.7%; early

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HAART reduced the risk 3-fold to 5.2%.¹⁸ To date, most infants diagnosed with dBCG disease were not on HAART or were started on HAART shortly before presentation. These findings highlight the importance of early infant HIV diagnosis and the potential of early HAART in reducing the risk of BCG-related adverse events.

Risk in context

In 2006 the prevalence of HIV infection among pregnant South African women in the public sector was 29.4%¹⁹ and the annual incidence of tuberculosis was 940 per 100 000.²⁰ In the Western Cape Province, the HIV-infected infant population at risk of developing serious BCG adverse events constituted approximately 1% of the total infant population ≤ 1 year of age during 2006.⁸ With a provincial maternal HIV prevalence of 15.2% and documented vertical transmissions rate of 5.4%, we predicted 804 HIV-infected infants in 2006.⁸ Provided the maternal seroprevalence remains stable, the infant population at risk is likely to remain stable or decline. Vertical transmission rates in other provinces of South Africa are considerably higher, reflecting the need to strengthen prevention of mother-to-child transmission (PMTCT) programmes nationally. However, HIV-infected infants (≤ 12 months of age) remain a small minority of all South African infants.

South African HIV-infected infants have a 20-fold higher risk of developing culture-confirmed tuberculosis disease compared with HIV-uninfected infants.²¹ There is no evidence of an excessive increase in disseminated tuberculosis compared with pulmonary tuberculosis in HIV-infected compared with uninfected infants.²¹ On the basis of the current evidence, the benefits of potentially preventing severe tuberculosis appear to be outweighed by the serious risks of BCG vaccine in the minority of HIV-infected infants, while in HIV-uninfected infants there is clear evidence of BCG benefits. No data exist regarding strategies to prevent tuberculosis in HIV-infected children who have not received BCG vaccination.

Challenges to implementation of revised BCG policy

There are potential risks of non-BCG vaccination in HIV-exposed uninfected and HIV-unexposed infants. South African HIV-exposed infants have a high risk of exposure to tuberculosis early in life.²² Factors indicated by the WHO as requiring consideration when assessing the risk for HIV infection and implementing the GACVS recommendations include the prevalence of tuberculosis and the potential for infant exposure to *Mycobacterium tuberculosis*, prevalence of HIV infection, coverage and efficacy of PMTCT interventions (including early infant diagnosis), rates of exclusive and mixed breastfeeding, and the capacity to conduct follow-up of immunised children. Other important considerations include



good surveillance systems for tuberculosis and HIV, and good services for infant immunisation, child health, and treatment of HIV-infected children.

A key consideration is the ability of infant vaccination and PMTCT programmes to allow for selectively delaying vaccination from birth until, for example, 10 - 14 weeks of age, following a negative HIV PCR testing result, e.g. at 4 - 6 weeks of age, and retaining infants for follow-up and vaccination when confirmed to be HIV-uninfected. In the Western Cape province, attendance for 14-week EPI vaccination visits was 81.3% during 2005, indicating potential loss to follow-up of approximately 20% during the first 14 weeks of life even in this well-functioning programme. Selectively delayed BCG vaccination strategies in HIV-exposed infants could be combined with alternative strategies such as isoniazid preventive therapy in the intervening period. Although the available data do not demonstrate a benefit of primary isoniazid preventive therapy in the absence of a documented tuberculosis contact among HIV-exposed uninfected or HIV-infected South African infants who received BCG at birth,²³ isoniazid preventive treatment is recommended in all infants who have a tuberculosis contact or proof of *M. tuberculosis* infection.

Envisioned impact of policy change in South Africa

Apart from reducing the considerable risk of BCG vaccination in a small proportion of HIV-infected infants, there is a potentially greater risk that the much larger proportion of HIV-exposed yet uninfected infants will inadvertently not receive BCG if vaccination is selectively deferred. In South Africa such inadvertent non-vaccination of HIV-exposed uninfected infants may predispose them to an increase in disseminated tuberculosis.

As PMTCT programmes are strengthened, the number of paediatric HIV infections should decline, resulting in an even smaller number of HIV-infected infants at risk of dBCC compared with a much larger pool of HIV-exposed uninfected and HIV-unexposed infants, who benefit from BCG vaccination. Early HIV testing and initiation of HAART in HIV-infected infants will soon be implemented in the Western Cape and it is hoped in the rest of South Africa, and will reduce all-cause mortality and the incidence of tuberculosis, BCG IRIS and possibly dBCC disease.

Do conditions necessary for implementation of selectively delayed BCG vaccination exist in South Africa?

Successful implementation of a selective delayed BCG vaccination policy in HIV-exposed infants requires that all of the following conditions be met:

- A high uptake of maternal HIV testing coupled with more effective PMTCT strategies including maternal HAART.
- Consistent screening and management of tuberculosis in pregnant women.
- Effective screening, diagnosis and management of tuberculosis in households with HIV-exposed infants.
- High retention of HIV-exposed infants in public health care programmes.
- Early virological diagnosis of HIV infection in infants with rapid turnaround time for results.
- Early institution of HAART in HIV-infected infants.
- Co-ordination of PMTCT, vaccination and tuberculosis programmes to: (i) ensure BCG vaccination of all HIV-uninfected infants; (ii) minimise loss to follow-up of all infants for vaccination and HIV testing; (iii) implement alternative tuberculosis preventive strategies; and (iv) deliver successful delayed vaccination following selective non-vaccination at birth.

These conditions do not currently exist in South Africa. Even where the required programmes are in place, major operational problems are present. Surveillance systems for tuberculosis and HIV and follow-up services for infants are often suboptimal. There is poor tuberculosis screening among HIV-infected pregnant women, who are at high risk of tuberculosis during the antenatal and postpartum periods.²⁴ The situation should improve with roll-out and strengthening of PMTCT and HAART programmes and integration of maternal and infant, HIV and tuberculosis programmes.

Paediatric public health practitioners, clinicians and researchers in paediatric tuberculosis and HIV, including the Western Cape Province Paediatric HIV/TB Policy Advisory Group, a provincial academic and public health technical advisory committee, and the International Union against Tuberculosis and Lung Diseases BCG Surveillance Working Group, have acknowledged the revised WHO recommendations.²⁵ However, there is consensus among these individuals and committees that universal BCG immunisation of infants should continue in South Africa and other developing countries with high burdens of HIV and tuberculosis until all programmes are in place for preventing maternal tuberculosis and HIV infection and for safely implementing selective deferred vaccination of HIV-exposed infants. Regular review should be done of programme implementation considerations and new available data. PMTCT programmes should be further strengthened to reduce the number of HIV-infected infants.

Conflict of interest. All authors: none declared.

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